

The effect of remifentanyl for reducing myoclonus during induction of anesthesia with etomidate

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Background: Myoclonic movement is a common problem during induction of anesthesia with etomidate. We investigated the influences of pretreatment with remifentanyl on etomidate induced myoclonus.

Methods: Ninety ASA class I patients were divided randomly into three groups. Group NS received normal saline 2 ml as placebo (n = 30), group R0.5 and group R1.0 were pretreated with remifentanyl 0.5 $\mu\text{g}/\text{kg}$ (n = 30) or 1.0 $\mu\text{g}/\text{kg}$ (n = 30) 1 minute before induction with etomidate 0.3 mg/kg. Orotracheal intubation was performed after administration of rocuronium 0.5 mg/kg. We assessed the incidence, onset, duration and intensity of myoclonus. Mean arterial pressure (MAP), heart rate (HR) and bispectral index (BIS) were recorded during induction.

Results: Twenty five patients developed myoclonus in group NS (83.3%), 3 patients in group R0.5 developed myoclonus (10%), as did 5 patients in group R1.0 (16.7%). Moderate to severe myoclonus of grade 3 and 4 were found 66.7% of patients in group NS, whereas no patients in both remifentanyl pretreated groups developed this grade of myoclonus. The duration of myoclonus was reduced significantly in the remifentanyl groups: 93.8 ± 59.5 sec in group NS, 49.3 ± 34.9 sec in group R0.5, 36.0 ± 27.0 sec in group R1.0 ($P < 0.05$). HR was decreased by pretreatment with remifentanyl prior to induction, while MAP and HR were decreased after induction with etomidate ($P < 0.05$). BIS changes were not different among the three groups. The dose dependent differences between the two remifentanyl doses were not noticed.

Conclusions: Pretreatment with remifentanyl significantly reduced the incidence, duration and intensity of etomidate induced myoclonus. (Korean J Anesthesiol 2009; 57: 438~43)

Key Words: Etomidate, Myoclonus, Pretreatment, Remifentanyl.

INTRODUCTION

Etomidate is a short-acting GABA (γ -aminobutyric acid) receptor-stimulating hypnotic agent causing minimal histamine release and a very stable hemodynamic profile [1-3], however up to 80% of patients who are not premedication experience myoclonus that is a serious problem in patients with open

globe injury or in non-fasting condition or limited cardiovascular reserve [3,4].

Previous researches have presented that a pretreatment with fentanyl reduces myoclonic movement and pain during the induction of anesthesia with etomidate. But alfentanil and buprenorphine do not have any better efficiency in preventing myoclonus [1,3]. Fentanyl stimulates μ -opioid receptor on GABA-nergic neurons in basal ganglia, which is known to decrease myoclonus [1,5,6]. These agents are suitable for long surgical procedure [4,5].

Remifentanyl, as a μ -opioid receptor agonist, exhibits similar potency to fentanyl and it has a rapid onset of analgesic action (1 min) and a fast offset of action (3–10 min), and does not release histamine [7-9]. Furthermore, it produces fewer cardiovascular changes if small doses are used [7]. Considering the strengths, remifentanyl is effectively used as a part of propofol-based total intravenous anesthesia or in combination with volatile anesthetics without prolonged recovery from anesthesia.

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The purpose of this study was to know the reducing effect of remifentanyl on myoclonus, and to compare the changes of mean arterial pressure (MAP), heart rate (HR) and bispectral index (BIS) during induction of anesthesia with etomidate.

MATERIALS AND METHODS

After obtaining approval by our Institutional Review Board and informed written consents from all participating patients, a prospective, randomized, double-blind study was performed.

Ninety American Society of Anesthesiologists physical status I patients scheduled for elective plastic surgery were selected as subjects (Table 1). Patients with neurologic, cardiopulmonary or endocrine disease, those with known drug hypersensitivity, and those who were anticipating difficult intubation were excluded. Remifentanyl to be used for this experiment was prepared after diluting with normal saline to 20 $\mu\text{g/ml}$ outside the operating room by an anesthesiologist not involved in induction of anesthesia. In the operating room, electrocardiogram, pulse oximeter and noninvasive arterial blood pressure were monitored.

A standard BIS monitor strip (BIS A-2000, Aspect medical systems Inc., USA) was placed on the patients' forehead. Intravenous (IV) glycopyrrolate 0.2 mg was given to each patient as a premedicant after confirming the IV route in dorsum hand with 18-gauge cannula.

Subsequently preoxygenation was performed with 100% O₂ using face mask. After patient's vital signs were virtually unchanged, we recorded their MAP, HR, BIS data as a baseline values.

The patients were randomly allocated to three groups. Group NS received normal saline 2 ml, group R0.5 received re-

mifentanyl (Ultiva[®], Glaxo Smith Kline, Italy) 0.5 $\mu\text{g/kg}$, group R1.0 received remifentanyl 1.0 $\mu\text{g/kg}$ intravenously.

The solutions were prepared in unlabeled syringes and handed to the anesthesiologist who was blind to the identity of the drug. After 1 minute interval, etomidate 0.3 mg/kg (Etomidate-Lipuro[®], B.Braun Melsungen, Germany) was injected intravenously over 30 seconds for induction. Rocuronium 0.5 mg/kg was given in order to facilitate orotracheal intubation and anesthesia initiated with sevoflurane 2% with 100% O₂ 4 L/min with manual ventilation using face mask.

Myoclonus was assessed visually, when presented, onset and duration were recorded and intensity of myoclonus was graded by a trained physician who was blind to the pretreated solution. Myoclonus was defined as involuntary, short contraction of some muscle fibers, of a whole muscle, or of different muscles of one group. For intensity measurements, a 4-point scale, validated by Holdcroft et al. [10] was used. Grade 1 = no movement, 2 = mild (involuntary movement at small unit of muscle group), 3 = moderate (movement in large or two muscle groups or mild generalized response), 4 = severe (generalized response or intense movement in two or more muscle groups). Orotracheal intubation was performed 3 minutes after administration of rocuronium. Anesthesia was maintained with sevoflurane 2 vol% and N₂O 2 L/min and O₂ 2 L/min.

Patients' MAP, HR, BIS were recorded before each drug trials, 1 min after the drug trials, 1 min after the induction with etomidate. For any further change, they were recorded immediate and 2, 4, 6 min after intubation.

Data were reported as number of patients (%) for categorical variables, mean \pm SD for normally distributed data. SPSS 12.0 for Windows software was used for statistical analysis. χ^2 (Chi-square) test was used to compare categorical variables between the groups and repeated measured ANOVA test, to compare the changes of BP, HR and BIS. If the P value obtained from a paired sample t-test was $p < 0.05$, it was considered as holding statistical significance.

RESULTS

There were no significant differences among the groups in age, weight, height and sex (Table 1). The incidence and duration of etomidate induced myoclonus were decreased significantly in both remifentanyl groups than in normal saline group (Table 2).

Though the onset of myoclonus did not vary among the three groups, the intensity of myoclonus significantly decreased

Table 1. Demographic Data

Group	Group NS (n = 30)	Group R0.5 (n = 30)	Group R1.0 (n = 30)
Sex (M/F)	14/16	15/15	16/14
Age (yr)	36.7 \pm 11.7	32.4 \pm 6.9	34.5 \pm 13.1
Height (cm)	165.5 \pm 9.4	168.8 \pm 6.9	166.5 \pm 10.7
Weight (kg)	62.0 \pm 9.2	63.9 \pm 10.7	65.9 \pm 10.5

All values except sex are mean \pm SD. There are no statistical differences among the three Groups. Group NS: received normal saline 2 ml, group R0.5: pretreated with remifentanyl 0.5 $\mu\text{g/kg}$, Group R1.0: pretreated with remifentanyl 1.0 $\mu\text{g/kg}$ before etomidate induction.

Table 2. Incidences of Myoclonus

Group	Group NS (n = 30)	Group R0.5 (n = 30)	Group R1.0 (n = 30)
Incidence of myoclonus	83.3%	10%*	16.7%*
Number of patients with myoclonus (Grade 1/2/3/4)	25 (5/5/10/10)	3 (2/3/0/0)	5 (2/5/0/0)
Onset of myoclonus (sec)	41.7 ± 31.4	50.7 ± 49.7	38.0 ± 32.1
Duration of myoclonus (sec)	93.8 ± 59.5	49.3 ± 34.9*	36.0 ± 27.0*

All values are mean ± SD except for the incidence of myoclonus and No. of patients. Group NS: received normal saline 2 ml, Group R0.5: pretreated with remifentanyl 0.5 µg/kg, Group R1.0: pretreated with remifentanyl 1.0 µg/kg before etomidate induction. *P < 0.05 compared with group NS.

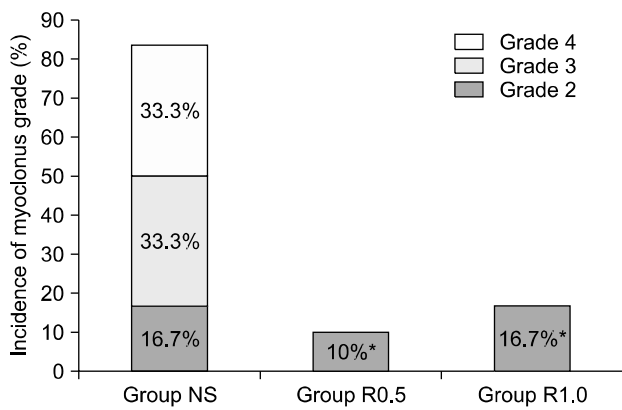


Fig. 1. Incidence of myoclonus (%). Group NS: received normal saline 2 ml, Group R0.5: pretreated with remifentanyl 0.5 µg/kg, Group R1.0: pretreated with remifentanyl 1.0 µg/kg before etomidate induction. In group R0.5 and group R1.0, the incidence and intensity of myoclonus significantly decreased compared with group NS. *P < 0.05 compared with group NS.

in remifentanyl groups (P < 0.05) (Table 2). In both of the remifentanyl groups developed only grade 2 myoclonus, whereas 66.7% of group NS developed grade 3 or 4 myoclonus (Fig. 1).

In addition, the remifentanyl groups indicated decreased MAP, when measured 1 min after etomidate induction (P < 0.05) (Fig. 2). Heart rates of both remifentanyl groups decreased when measured not only 1 min after receiving remifentanyl but also 1 min after induction with etomidate (P < 0.05) (Fig. 3). There were no cases of hypotension or bradycardia.

BIS was not different significantly among the three groups at all time points (Fig. 4). The dose dependent effects of remifentanyl 0.5 µg/kg and 1.0 µg/kg were not significantly noticed at all measurements.

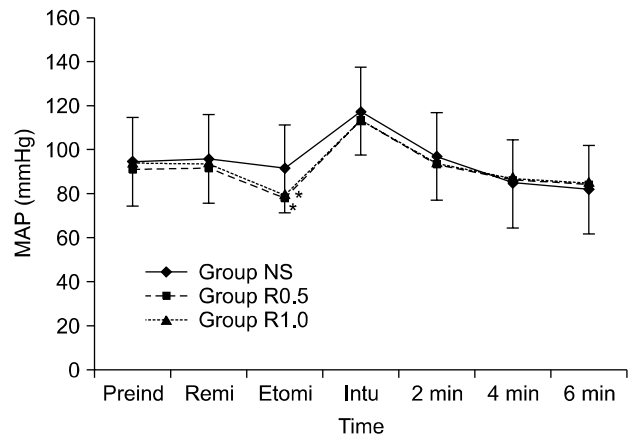


Fig. 2. Changes in mean arterial pressure (MAP). Group NS: received normal saline 2 ml, Group R0.5: pretreated with remifentanyl 0.5 µg/kg, Group R1.0: pretreated with remifentanyl 1.0 µg/kg before etomidate induction. Preind: before induction time, Remi: 1 min after receiving saline or remifentanyl, Etomi: 1 min after induction with etomidate 0.3 mg/kg, Intu: immediate after intubation, 2 min, 4 min, 6 min: 2, 4, 6 minutes after intubation. *P < 0.05 compared with group NS.

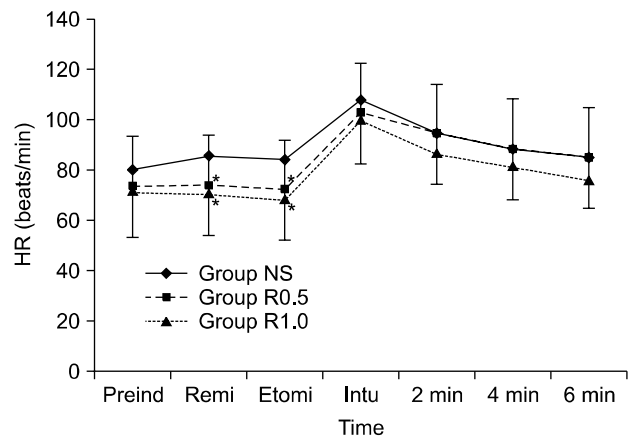


Fig. 3. Changes in heart rate (HR). Group NS: received normal saline 2 ml, Group R0.5: pretreated with remifentanyl 0.5 µg/kg, Group R1.0: pretreated with remifentanyl 1.0 µg/kg before etomidate induction. Preind: before induction time, Remi: 1 min after receiving saline or remifentanyl, Etomi: 1 min after induction with etomidate 0.3 mg/kg, Intu: immediate after intubation, 2 min, 4 min, 6 min: 2, 4, 6 minutes after intubation. *P < 0.05 compared with group NS.

DISCUSSION

Previous studies reported that remifentanyl 1.0 µg/kg reduces the myoclonus incidence after etomidate 0.3 mg/kg injection [4]. In general, the minimal bolus dose of remifentanyl is 0.5 µg/kg,

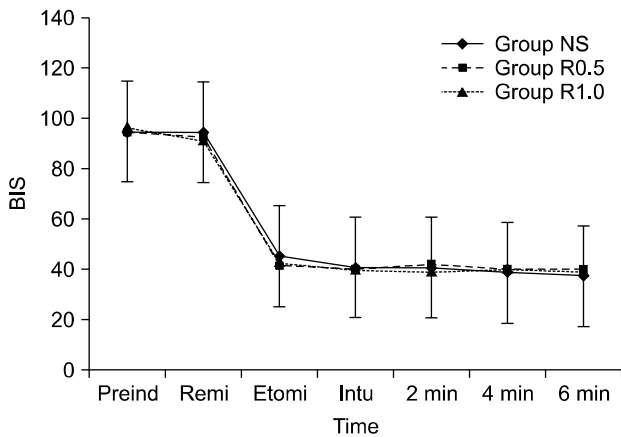


Fig. 4. Changes of BIS. There are no significant differences among the three groups. Group NS: received normal saline 2 ml, Group R0.5: pretreated with remifentanil 0.5 $\mu\text{g}/\text{kg}$, Group R1.0: pretreated with remifentanil 1.0 $\mu\text{g}/\text{kg}$ before etomidate induction. Preind: before induction time, Remi: 1 min after receiving saline or remifentanil, Etomi: 1 min after induction with etomidate 0.3 mg/kg, Intu: immediate after intubation, 2 min, 4 min, 6 min: 2, 4, 6 minutes after induction.

and the recommended loading bolus dose of remifentanil during anesthesia induction with standard hypnotic agent (propofol, thiopental or isoflurane) is 1.0 $\mu\text{g}/\text{kg}$ [8]. Moreover, remifentanil has rapid blood-brain equilibration time, between 1.0 and 1.5 minutes and has short context-sensitive half time as 3–5 minutes [11]. In these reasons, the present study administered remifentanil at the time of 1 minute prior to induction with etomidate and we used two bolus doses of remifentanil 0.5 $\mu\text{g}/\text{kg}$ and 1.0 $\mu\text{g}/\text{kg}$, but dose-dependent differences of remifentanil on reducing myoclonus were not noticeable.

There are some factors known to affect the occurrences of myoclonus, such as age, gender of a patient and dosages of the etomidate [4,12]. In male, the incidence is 50–87.5%, however 50% in female, 11% in patients older than 60 years [4,6]. Reddy et al. [13] investigated the excitatory movement including myoclonus, tremor and dystonic posture, occurred in 86.6% of patients receiving etomidate (mean age 66.1 yr) and 100% in children.

Moreover, the development of myoclonus is dose dependently different. The recommended induction dose of etomidate is usually 0.3–0.4 mg/kg, and for Korean women is approximately 0.2 mg/kg [12,14]. The relatively higher doses of etomidate and younger ages of the subjects (average age of thirties) might have possibly affected our results, so the incidences and intensities of myoclonus were appeared somewhat higher.

The neurologic mechanism of myoclonus is unclear but one of the most possibilities is a disinhibition phenomenon of subcortical structure. That is etomidate depresses cortical activity before it depresses subcortical activity [6,13], thus depresses the inhibitory neural circuits prior to excitatory circuits and not caused by an epileptic focus [3,6,12]. The basis of this theory is that the excitatory phenomenon of myoclonus is caused by disequilibrium of the drug at the various target sites in the central nervous system. Differences in local cerebral blood flow or affinity might produce a temporary disequilibrium of effect, resulting in more rapid depression of cortical inhibition [6,12].

In addition, high concentration of etomidate interacts with GABA_A receptors of central nervous reticular activating system. With interruption of GABA neurons, pathways associated with skeletal muscle control can become more sensitive, allowing spontaneous nerve transmissions. These events can ultimately lead to myoclonic muscle contraction [5,6]. For these ethical reasons, myoclonus can be prevented when premedication with benzodiazepines, fentanyl or others known to inhibit subcortical neuronal activity [3,6]. Pretreatment with opioids reduced myoclonus and pain during induction of anesthesia with etomidate. Pretreatment with fentanyl (100, 250, 500 μg) reduced the incidence of myoclonus (33%, 13%, 0%) but increased the incidence of apnea (87%, 87%, 100%) during induction [1,4].

Etomidate antagonizes the N-methyl-D-aspartate (NMDA) receptor directly, resulting in cerebral protection. NMDA as a glutamic acid derivative induces the release of large amounts of glutamate that can cause cell death during brain injury. Hence it is reported that one of the important mechanism of cerebral protection is to inhibit the release of glutamate [15]. Pretreatment with NMDA receptor antagonists such as magnesium sulfate (Mg) can effectively prevent etomidate induced myoclonus but not in case with ketamine [3]. Mg and ketamine may attenuate withdrawal movements or pain caused by various chemical mediators either in vascular endothelium or in the brain and the dorsal horn of the spinal cord [3,16]. NMDA receptor agonist such as remifentanil induces the Ca⁺⁺ influx, and result in production of nitric oxide (NO). This NO has an important role in development of postoperative pain and opiate tolerance [16]. Thus, the interaction of remifentanil and etomidate on NMDA receptors would need more investigations.

As for remifentanil, it produces minimal effects on the cardiovascular system with an expected mild bradycardia and 15–20% decreases in arterial pressure. However, that could be

mostly prevented through premedication with glycopyrrolate [7,8]. Meanwhile, etomidate decreases peripheral vascular resistance which is responsible for a slight decline in arterial blood pressure. Myocardial contractility and cardiac output remain unchanged [17]. We found that etomidate did not affect the MAP and HR during induction. Remifentanyl 0.5 $\mu\text{g}/\text{kg}$ and 1.0 $\mu\text{g}/\text{kg}$ significantly decreased HR only before induction. After etomidate administration, both HR and MAP were decreased significantly (Fig 2, 3). Previous researches reported that remifentanyl 1 $\mu\text{g}/\text{kg}$ bolus followed by an infusion 0.5 $\mu\text{g}/\text{kg}/\text{min}$ during anesthetic induction attenuate the hemodynamic response to laryngoscopy and tracheal intubation [18,19]. We thought that bolus doses of remifentanyl 0.5 and 1.0 $\mu\text{g}/\text{kg}$ before the induction did not effectively attenuate the hemodynamic responses to intubation, because of its very short duration of action and short elimination time. (Fig 2, 3).

BIS has been used as an indicator of measuring hypnotic effect of anesthetics and sedatives [20-22]. A BIS value of 50 was appropriate during tracheal intubation following etomidate induction. Myoclonus did not cause epileptic paroxysms or ictal spiking likely to alter BIS [21]. A BIS is derived from the EEG and reflects cortical activity, thus BIS cannot be considered a true reflection of the depth of anesthesia [22,23]. Our study demonstrated that remifentanyl did not affect the changes of BIS. We assumed that it was caused by sudden decreased BIS after administration of hypnotic dose of etomidate could not reflect the effect of remifentanyl (Fig. 4). In opioids, almost 5 times the analgesic concentrations would be required for the appearance of a noticeable EEG depression and analgesic concentrations of opioids produce minimal or no EEG alteration on cerebral cortex. If BIS suddenly increases in response to a noxious stimulus, this could be a cortical arousal reaction reflecting a deficit in the analgesic component [22]. Our study demonstrated the BIS did not reflect the painful stimulus such as intubation, because the pain is subcortical activity not cortical component.

In conclusion, a bolus injection of remifentanyl 1 min before induction of anesthesia with etomidate significantly decreased the incidence, duration and intensity of myoclonus without development of hypotension and bradycardia. In addition, a dose dependent effect of remifentanyl 0.5 $\mu\text{g}/\text{kg}$ and 1.0 $\mu\text{g}/\text{kg}$ were not noticed. We expect that our results will be helpful during induction with etomidate and remifentanyl in patients with poor cardiac reserve.

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